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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/622,293	07/17/2003	Toby Freyman	10177-118-999	5795

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EXAMINER	
NGUYEN, QUANG	

ART UNIT	PAPER NUMBER
1633	

DATE MAILED: 11/21/2005

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	10/622,293	FREYMAN ET AL.	
	Examiner	Art Unit	
	Quang Nguyen, Ph.D.	1633	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *19 September 2005*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-41* is/are pending in the application.

4a) Of the above claim(s) *3,4,16-26,29,31-34 and 36-41* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1,2,5-15,27,28,30 and 35* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date *3/8/04; 11/15/04*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

Claims 1-41 are pending in the present application.

Applicant's election of Group I (Claims 1-2, 5-15, 27-28, 30 and 35, drawn to a method for producing a decellularized extracellular matrix material containing a biological material or for producing a tissue regeneration scaffold for implantation into a patient wherein the step of conditioning a body tissue of a donor animal by genetic engineering and allowing the conditioned body tissue to produce the biological material are conducted prior to harvesting the conditioned body tissue from the donor animal) in the reply filed on 6/17/05 is acknowledged. Because applicant did not distinctly and specifically point out the supposed errors in the restriction requirement, the election has been treated as an election without traverse (MPEP § 818.03(a)).

Applicants further elected the following species with traverse in the reply filed on 9/19/05, (a) bone marrow as a species of a body tissue; (b) VEGF as a species of a biological material; and (c) human as a species of a donor animal. Once again, because applicant did not distinctly and specifically point out the supposed errors in the species restriction requirement, the election has been treated as an election without traverse (MPEP § 818.03(a)).

Therefore, claims 3-4, 16-26, 29, 31-34 and 36-41 are withdrawn from further consideration because they are directed to non-elected inventions.

Accordingly, claims 1-2, 5-15, 27-28, 30 and 35 are examined on the merits herein with the aforementioned elected species.

Specification

The abstract of the disclosure is objected to because it exceeds 150 words. Correction is required. See MPEP § 608.01(b).

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 1-2, 5-15, 27-28, 30 and 35 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the enablement requirement **with respect to the elected invention and elected species**. The claim(s) contains subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.

The factors to be considered in the determination of an enabling disclosure have been summarized as the quantity of experimentation necessary, the amount of direction or guidance presented, the state of the prior art, the relative skill of those in the art, the predictability or unpredictability of the art and the breadth of the claims. *Ex parte Forman*, (230 USPQ 546 (Bd Pat. Appl & Unt, 1986); *In re Wands*, 858 F.2d 731, 8 USPQ 2d 1400 (Fed. Cir. 1988)).

(a) The breadth of the claims

With respect to the elected invention and elected species, the instant claims are drawn to a method for producing a decellularized extracellular matrix material containing VEGF or for producing a tissue regeneration scaffold for implantation into a patient, wherein the method comprises: (a) conditioning bone marrow of human donor to produce VEGF in an amount different than the amount of VEGF that the bone marrow would produce absent the conditioning by transfecting the bone marrow with any nucleic that encodes VEGF by any route of administration at any site in the human donor; (b) allowing the conditioned bone marrow to produce the VEGF; then (c) harvesting the conditioned bone marrow from the human donor; and (d) decellularized the conditioned bone marrow to obtain the extracellular matrix material containing the VEGF. When read in light of the specification, the sole purpose for a method of producing a decellularlized extracellular matrix material containing a biological material is for treatment purpose in repairing, regenerating or strengthening tissue or organs *in vivo* (see instant specification, at least page 3, lines 7-18; page 5, line 3 continues to line 5 of page 6). Please note that enablement requires the specification to teach a skilled artisan on how to make and/or **USE** the invention.

(b) The state and the unpredictability of the art

At the filing date of the present application, virtually nothing was known in the prior art for genetically modifying bone marrow of a human donor *in vivo* with any nucleic acid encoding any biological material, including VEGF, and subsequently decellularizing the harvesting the genetically modified bone marrow and using the conditioned and acellular extracellular matrix for repairing, regenerating or

strengthening tissue or organs *in vivo*. Moreover, at the filing date of the present application the attainment of any therapeutic effect in any patient via gene therapy was, and remains highly unpredictable. There are several known factors that limit an effective human gene therapy, including sub-optimal vectors, the lack of a stable and effective *in vivo* transgene expression that yield a therapeutic effect, the adverse host immunological responses to the delivered vectors and most importantly an efficient gene delivery to target tissues or cells as supported at least by the teachings of Verma et al. (Nature 389:239-242, 1997), Dang et al. (Clin. Cancer Res. 5:471-474, 1999) and Romano et al. (Stem Cells 18:19-39, 2000). Even in 2005, Verma et al. (Annu. Revi. Biochem. 74:711-738, 2005) still state "The young field of gene therapy promises major medical progress toward the cure of a broad spectrum of human diseases, ranging from immunological disorders to heart disease and cancer. It has, therefore, generated great hopes and great hypes, but **it has yet to deliver its promised potential**", and "[I]f scientists from many different disciplines participate and pull together as a team to tackle the obstacles, **gene therapy will be added to our medicinal armada** and the ever-expanding arsenal of new therapeutic modalities." (page 732, top of third paragraph). Goncalves (BioEssays 27:506-517, 2005) also states "Overall, one can conclude that **further improvements in gene transfer technologies** (e.g. control over transgene expression and integration) and **deeper insights in host-vector interactions** (e.g. knowledge on vector and gene-modified cell biodistribution following different routes of administration and the impact on innate and adaptive immunity) are

warranted before clinical gene therapy reaches maturity" (page 514, right-hand column, last paragraph).

(c) The amount of direction or guidance presented

The instant specification fails to provide any guidance for a skilled artisan on how to overcome the hurdle of *in vivo* vector targeting to desired tissues/organs, for this instance to the human bone marrow tissue, by any route of delivery and/or at any site in the human donor so that an efficient gene delivery can be attained in the human bone marrow tissue. There is no evidence in either the prior art or in the instant disclosure that any nucleic acid encoding a biological material such as VEGF is capable of transfecting a sufficient number of resident cells in the human bone marrow to produce an effective amount of the biological material to be incorporated in the bone marrow, so that the subsequently harvested and decellularized extracellular matrix can yield any therapeutic effect in repairing, regenerating or strengthening tissue or organs *in vivo* as contemplated by Applicants. Particularly, in light of the unpredictability and the difficulty for attaining an effective level of any transgene expression *in vivo* that yields a therapeutic effect as indicated by the gene therapy art that was discussed above.

With the lack of sufficient guidance provided by the present application, and in light of the state of the art at the filing date of the present application, it would have required undue experimentation for a skilled artisan to make and use the elected invention.

(d) Working example provided

There is an absence of an example demonstrating that any therapeutic effect has been attained or achieved for a genetically modified and acellular human bone marrow extracellular matrix produced by the elected invention.

Accordingly, due to the lack of sufficient guidance provided by the specification regarding to the issues discussed above, the unpredictability of the physiological art and particularly the attainment of an effective transgene expression *in vivo* that produces any therapeutic effect, and the breadth of the instant claims, it would have required undue experimentation for one skilled in the art to make and use the instant elected claimed invention.

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

Claims 1, 5, 7-12, 14-15, 27 and 35 are rejected under 35 U.S.C. 102(b) as being anticipated by Naughton (US 5,830,708; IDS).

The claims are directed to a method for producing a decellularized extracellular matrix material containing a biological material or for producing a tissue regeneration scaffold for implantation into a patient having the steps recited in independent claims 1, 27 and 35 without any particular order of the steps.

Naughton teaches a method for producing a composition containing naturally secreted human extracellular matrix material, said method comprises the steps of: (a) culturing extracellular matrix secreting human stromal cells from tissues/organs obtained by appropriate biopsy or upon autopsy, including aspirated bone marrow from normal human adult volunteers (col. 5, lines 48-54; col. 15, lines 7-9), on a biocompatible three dimensional framework *in vitro*; (b) the stromal cells are killed after secretion of the extracellular matrix onto the framework and the cells and cellular contents are removed from the framework resulting in a scaffold containing a decellularized extracellular matrix (col. 11, line 62 continues to line 63 of col. 12); (c) the extracellular matrix material deposited on the framework is collected and further processed to obtain a physiologically acceptable composition (col. 12, line 66 continues to line 20 of col. 14). Naughton further teaches that it may be desirable to prepare an extracellular matrix containing a foreign gene product, growth factor, regulatory factor and in such a situation the cells are genetically engineered to express the gene product that is immobilized in the extracellular matrix laid down by the stromal cells (col. 10, line 59 continues to line 22 of col. 11). This is a conditioning step. Naughton teaches that preferably, the expression control elements used should allow for the regulated expression of the gene so that the product can be over-synthesized in culture (col. 11, lines 15-17). Furthermore, Naughton teaches that biologically active substances such as proteins and drugs can also be incorporated in the composition for release or controlled release of these active substances after injection of the composition that include tissue growth factors such as TGF-beta and the like which promote healing and

tissue repair at the site of injection (col. 13, lines 12-22). Naughton teaches that the extracellular matrix preparation is capable of promoting connective tissue deposition, angiogenesis, reepithilialization and fibroplasias, which is useful in the repair of skin and other tissue defects, and that the preparation is used to repair tissue defects by injection at the site of the defect (col. 3, lines 43-48; col. 13, line 43 continues to line 20 of col. 14).

It is noted that the term "body tissue" is defined by the instant specification broadly encompasses any or a number of cells, tissues or organs (see page 7, lines 7-8). Accordingly, the teachings of Naughton meet all the limitation of the instant claims as broadly written.

Therefore, the instant claims are anticipated by Naughton (US 5,830,708; IDS).

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was

not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

Claims 1, 13, 27 and 30 are rejected under 35 U.S.C. 103(a) as being unpatentable over Naughton (US 5,830,708; IDS) in view of Herlyn et al. (WO 98/39035).

Naughton teaches a method for producing a composition containing naturally secreted human extracellular matrix material, said method comprises the steps of: (a) culturing extracellular matrix secreting human stromal cells from tissues/organs obtained by appropriate biopsy or upon autopsy, including aspirated bone marrow from normal human adult volunteers (col. 5, lines 48-54; col. 15, lines 7-9), on a biocompatible three dimensional framework *in vitro*; (b) the stromal cells are killed after secretion of the extracellular matrix onto the framework and the cells and cellular contents are removed from the framework (col. 11, line 62 continues to line 63 of col. 12); (c) the extracellular matrix material deposited on the framework is collected and further processed to obtain a physiologically acceptable composition (col. 12, line 66 continues to line 20 of col. 14). Naughton further teaches that it may be desirable to prepare an extracellular matrix containing a foreign gene product, growth factor, regulatory factor and in such a situation the cells are genetically engineered to express the gene product that is immobilized in the extracellular matrix laid down by the stromal cells (col. 10, line 59 continues to line 22 of col. 11). This is a conditioning step. Naughton teaches that preferably, the expression control elements used should allow

for the regulated expression of the gene so that the product can be over-synthesized in culture (col. 11, lines 15-17). Furthermore, Naughton teaches that biologically active substances such as proteins and drugs can also be incorporated in the composition for release or controlled release of these active substances after injection of the composition that include tissue growth factors such as TGF-beta and the like which promote healing and tissue repair at the site of injection (col. 13, lines 12-22). Naughton teaches that the extracellular matrix preparation is capable of promoting connective tissue deposition, angiogenesis, reepithilialization and fibroplasias, which is useful in the repair of skin and other tissue defects, and that the preparation is used to repair tissue defects by injection at the site of the defect (col. 3, lines 43-48; col. 13, line 43 continues to line 20 of col. 14). It should be noted that the term "body tissue" is defined by the instant specification broadly encompasses any or a number of cells, tissues or organs (see page 7, lines 7-8).

Naughton does not specifically teach that the human stromal cells from bone marrow are genetically modified to express VEGF, even though Naughton teaches that it may be desirable to prepare an extracellular matrix containing any foreign gene product and any growth factor to be immobilized in the extracellular matrix laid down by the stromal cells (col. 10, line 59 continues to line 22 of col. 11).

However, at the effective filing date of the present application Herlyn et al already teach growth factors, particularly VEGF is useful in wound repair in mammalian tissue by enhancing fibroblast growth and formation into a matrix, enhancing keratinocyte growth and angiogenesis and *ex vivo* method for infecting tissue to be transplanted with

a recombinant virus expressing VEGF prior to transplantation (at least page 6, lines 14-23).

Accordingly, it would have been obvious for an ordinary skilled artisan in the art to modify the method of Naughton by specifically genetically modifying stromal cells derived from human bone marrow with a recombinant virus expressing VEGF, so that the exogenous gene product is immobilized in the extracellular matrix laid down by the stromal cells in light of the teachings of Herlyn et al.

An ordinary skilled artisan would have been motivated to carry out the above modification because Herlyn et al already teach growth factors, particularly VEGF is useful in wound repair in mammalian tissue by enhancing fibroblast growth and formation into a matrix, enhancing keratinocyte growth and angiogenesis, and that this would enhance the clinical value for the composition containing naturally secreted human extracellular matrix material of Naughton.

An ordinary skilled artisan would have a reasonable expectation of success to carry out the above modification in light of the teachings of Naughton and Herlyn et al., coupled with a high level of skills of an ordinary skilled artisan in the relevant art.

Therefore, the claimed invention as a whole was *prima facie* obvious in the absence of evidence to the contrary.

Conclusion

No claims are allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Quang Nguyen, Ph.D., whose telephone number is (571) 272-0776.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's primary, Celine Qian, Ph.D., may be reached at (571) 272-0777, or SPE, Dave Nguyen, at (571) 272-0731.

To aid in correlating any papers for this application, all further correspondence regarding this application should be directed to Group Art Unit 1633; Central Fax No. (571) 273-8300.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to (571) 272-0547.

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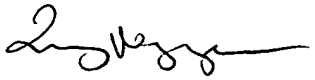

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